REMARKS

A check for the fees for a three month extension of time and Notice of Appeal accompanies this response. A Notice of Appeal also accompanies this response. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. **06-1050**. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. **06-1050**. Applicant's "Response" filed June 18, 2003, responsive to the previous Office Action mailed December 18, 2002, is incorporated by reference herein.

Claims 23-60 are pending in the instant application.

THE REJECTION OF CLAIMS 23-60 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 23-60 are rejected under 35 U.S.C. § 112, first paragraph, for reasons of record in the previous Office Action of December 18, 2002. The Examiner maintains that the specification does not reasonably provide enablement for producing transgenic animals by introducing a artificial chromosome or satellite artificial chromosome in any nuclear donor cell, transferring the nucleus of the nuclear donor cell into any enucleated recipient cell and transferring the recipient cell into any maternal host animal because the art of producing transgenic animals by nuclear transfer from any donor cell into any recipient cell and for transfer of artificial chromosomes into a cell that could serve as a donor cell was allegedly unpredictable.

Applicant's arguments responsive to the previous Office Action are deemed unpersuasive for the following reasons:

1) Responsive to Applicant's argument that the Examiner's reliance on post-filing date references to establish a lack of enablement is improper, it is alleged that the argument is not persuasive because publications that covered the state of the art from the date of filing of the application to the present were used to demonstrate that the state of the art of making a transgenic animal using the

method as claimed was not "predictable" and therefore the claimed subject matter is not enabled.

2) Responsive to case law cited by Applicant, it is alleged that the case law is "not relevant" because the "issue at hand" is enablement of the full scope of the subject matter as claimed where the state of the art is unpredictable. The Examiner then cites case law that allegedly stands for various propositions when the state of the art is unpredictable, such as: In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (..."if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling."); In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938) (..."in arts there the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims."); In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) and In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991) ([unpredictable because]..."it is not obvious from the disclosure of one species, what other species will work."); Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991) ("unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims").

3) Responsive to Applicant's argument that the disclosure of Wilmut *et al.* (1997) Nature 385:810-813), incorporated by reference in the specification, can be reproduced and there is no requirement in the law that the method must be fully reproducible every time it is practiced, the Examiner reiterates that the process of Wilmut *et al.* "has been found to be non-reproducible in the art" and since the specification does not provide a working example, one of skill in the art would not know whether the method will work in light of the art of record that indicates that the method was not reproducible. The Examiner further alleges that Applicant's arguments that the articles of Wolf *et al.* (*J. Biotechnol.*, 65:99-110 (1998)), cited by the Examiner, and Sgamarella *et al.* (*Science*,

279(51):635-636, (1998) cited in Wolf *et al.* and submitted by Applicant along with the previous response, do not demonstrate that undue experimentation would be required to practice the method of Wilmut *et al.*, are not persuasive because the specification allegedly does not teach how one of skill in the art would have corrected the alleged "problems" of the method of Wilmut *et al.* The Examiner further alleges that the article of Schnieke *et al.* (*Science*, 278:2130-2133, (1997); WO 02/062131), cited by Applicant in support of the argument that the Wilmut *et al.* method is reproducible, in fact did not "exactly follow" the method of Wilmut *et al.* because "the source of nuclei were different, the culture methods were different, *etc.*," and these "improvisations" are allegedly not taught in the specification.

4) Responsive to Applicant's discussion of the knowledge of those of skill in the art, it is alleged that Applicant has not demonstrated that the art of making transgenic animals by nuclear transfer involving introducing the gene of interest into a cell using artificial chromosomes was routine as of the application's earliest priority date. It is further alleged that none of the working examples in the specification teach how to make a transgenic animal as recited in the claimed methods.

In conclusion, the Examiner maintains that because the method of Wilmut *et al.* is "unpredictable," it is not an enabling disclosure and therefore the instant specification, which incorporates Wilmut *et al.* by reference, is also not enabling for transfer of artificial chromosomes into cells that could serve as donor cells and for producing transgenic animals by nuclear transfer.

This rejection is respectfully traversed.

Analysis

Summary of Arguments

Applicant's arguments responsive to the above rejection are presented in three sections, which are summarized as follows and discussed in detail following the summary:

A) Applicant has addressed each of the specific issues raised by the Examiner in the instant Final Office Action in rebuttal of Applicant's arguments responsive to the previous Office Action. These issues include, for example, the alleged unpredictability of the instantly claimed methods in light of the teachings of the specification, to the extent that the unpredictability alone allegedly provides reasonable doubt as to enablement of the methods as broadly claimed; and the alleged inadequate knowledge of those of skill in the art concerning the art of nuclear transfer.

In particular, the Examiner maintains that the specification is not enabling for the instant methods as claimed because the disclosure of Wilmut *et al.*, which is incorporated by reference in the instant application, is allegedly not enabled for a reproducible, "predictable" nuclear transfer method. To support his assertion, the Examiner alleges that Applicant has not demonstrated how to overcome the alleged "problems" of the method of Wilmut *et al.* that are pointed to in Wolf *et al.* because the article of Schnieke *et al.*, cited by Applicant in support of the argument that the Wilmut *et al.* method is reproducible, in fact did not "exactly follow" the method of Wilmut *et al.*

In response, and as discussed further below, Applicant points to experimental details in Schnieke *et al.* that follow the method of Wilmut *et al.* with, at most, extremely routine variations, and demonstrates the operability of the method of Wilmut *et al.* Moreover, Applicant respectfully submits that the Examiner, in maintaining that the method of Wilmut *et al.* is "non-reproducible" and "unpredictable," has failed to consider issued U.S. Patent No. 6,147,276, submitted by Applicant along with the previous response. U.S. Patent No. 6,147,276 is the issued patent corresponding to U.S. Application Serial No. 08/802,282, filed February 19, 1997, which is a continuation of PCT Application No. PCT/GB96/02099, published as WO 97/07669 and incorporated by reference in the instant application. Further, Wilmut *et al.*, published February 27, 1997, is a publication that is based on the disclosure of WO

97/07669. Because a U.S. Patent has issued with the same disclosure as WO 97/07669, and because a U.S. Patent is presumptively valid and enabled as of its filing date, the disclosure of WO 97/07669 is operative because claims that are based on the disclosure have issued in U.S. Patent No. 6,147,276.

Therefore, contrary to the Examiner's assertions regarding "non-reproducibility" of the method of nuclear transfer described in Wilmut *et al.*, it is respectfully submitted that Wilmut *et al.*, which is based on PCT Publication No. WO 97/07669, which in turn has the same disclosure as that of U.S. Patent No. 6,147,276, is presumed to be operative and reproducible because the issued U.S. patent is presumptively valid (35 U.S.C. 282). Furthermore, the instant specification is reproducible and operative for the methods as claimed because it describes and incorporates by reference the methods of nuclear transfer provided in International PCT Publication Nos. WO 97/07669 and Wilmut *et al.*

With regard to the knowledge of those of skill in the art with respect to nuclear transfer methods, as discussed below, it is respectfully submitted that the Examiner has failed to consider the various references (*see, e.g.*, Wells *et al.*, *Biol. Reprod.*, 57:385-393 (1997); Campbell *et al.* (1996) *Nature 380*:64-66; PCT Application Publication No. WO95/17500; Solter (1996) *Nature*, 380: 24-25; Sims *et al.* (1993), *Proc. Natl. Acad. Sci. USA*, 90:6143-6147; Tanaka *et al.* (1997) *Animal Reprod. Sci.*, 49:113-123) provided by Applicant that demonstrate the advanced state of the art of nuclear transfer methods and the production of transgenic animals therefrom at the earliest priority date of the instant methods or shortly thereafter.

B) In light of the above and the response filed June 18, 2003, which is incorporated by reference herein, Applicant respectfully maintains that an analysis of the factors enumerated in Ex parte Forman, including unpredictability, leads to the conclusion that the specification is enabling for the

full scope of the claimed methods because it would not require undue experimentation for one of skill in the art to practice the claimed methods.

This section concludes that the Examiner has failed to establish unpredictability and irreproducibility of the instantly disclosed and claimed methods of nuclear transfer, nor the lack of knowledge of nuclear transfer of those of skill in the art. Contrary to the Examiner's assertion and as discussed in detail below, Applicant has demonstrated that no more than routine experimentation is required to reproduce the teachings of the specification. Applicant has further demonstrated that the disclosures of Wilmut *et al.* and WO 97/07669 are presumptively reproducible and operative because there is an issued U.S. patent, presumptivel valid and enabled as of its filing date, that has the same disclosure as WO 97/07669 and Wilmut *et al.* is based on the disclosure in WO 97/07669. Furthermore, the method described in the specification, which incorporates by reference Wilmut *et al.* and WO 97/07669, is also therefore reproducible and operative. Applicant has also demonstrated that the art of nuclear transfer was well established as of the earliest priority date of the claims or shortly thereafter. Therefore, a consideration of the factors enumerated in Ex parte Forman, including predictability and the knowledge of those of skill in the art, leads to the conclusion that it would not require undue experimentation for one of skill in the art to practice the claimed methods.

A. Rebuttal to specific issues raised in the Final Office Action responsive to Applicant's previous response filed June 18, 2003

1) Post-filing date References cited by the Examiner

It is alleged that Applicant's argument regarding the Examiner's improper reliance on post-filing date references to establish a lack of enablement is not persuasive because the references were used to show that the "state of the art" from the date of filing of the application to the present date was "not predictable."

Applicant respectfully maintains that the issue with respect to lack of enablement is whether the specification, at the time of filing of the application, teaches one of skill in the art how to make and use the claimed subject matter without undue experimentation. In the previous response filed June 18, 2003, and herein, Applicant demonstrated that the specification provides extensive teachings of each of the steps of the method as claimed, and these teachings, when combined with the general knowledge of those of skill in the art at the time the application was filed regarding (1) DNA, including chromosome, introduction into cells; (2) nuclear transfer techniques; and (3) methods of generating transgenic animals; lead to the conclusion that one of skill in the art could carry out the instantly claimed methods without undue experimentation.

To the contrary, the post-filing date references cited by the Examiner, regardless of the fact that their citation to establish lack of enablement is inapt, provide no evidence of "unpredictability" of the instantly claimed methods. As discussed in the response filed June 18, 2003, the references cited by the Examiner in fact illustrate the promise of the technology of nuclear transfer and its commercial value even when the efficiency of the technique is low.

For example, Stice *et al.* (*Theriogeneology* 49:129-138, (1998)), which allegedly teaches the limitations of species-specific differences in animal cloning by nuclear transfer that led to only one example of a nuclear transfer pig, in fact is a review on the "power and capabilities" of nuclear transfer, the breakthroughs in nuclear transfer, and the commercial applications of cloning by nuclear transfer. Stice *et al.* discusses how the commercial use of nuclear transfer is not limited by inefficiencies in nuclear transfer procedures, because only a few cloned transgenic founder animals are needed (*see, e.g.*, page 133, "Commercial Applications of Cloning").

Yanagimachi (*Mol. Cell. Endocrin.* 187:241-248 (2002)), which allegedly teaches that no single protocol of nuclear transfer works for all species because the characteristics of oocytes and donor cells are different from species to

species, provides several examples of the successes in nuclear transfer (page 243, col. 2). Oback and Wells (*Cloning and Stem Cells*, 4:169-174, (2002)) provides detailed guidelines for donor cell selection, cell cycle synchronization and other parameters for nuclear transfer (see entire publication). The availability of such detailed guidelines as provided in Oback and Wells establishes predictability rather than unpredictability of the practice of nuclear transfer methods because the methods can be practiced without undue experimentation. Kuhholzer and Prather (*Soc. Exp. Biol. Med.*, 224:240-245, (2000)) discusses the promise of nuclear transfer as evidenced by the dramatic improvement in nuclear transfer protocols within the five preceding years, and how cloning and transgenic animal production have been greatly enhanced by the development of nuclear transfer technology (*see, e.g*, Abstract and page 244, col. 1).

The Co *et al.* (*Chromosome Res.*, 8:183-191, (2000)) reference cited by the Examiner, in addition to being an inapt citation of a post-filing date reference to establish lack of enablement, does not in any way address "predictability" of the methods as instantly claimed. It is respectfully submitted that the Examiner's reliance upon Co *et al.* is speculation that if, instead of the disclosed methods of pronuclear microinjection therein, they carry out a method of nuclear transfer, the use of the donor cell to produce a transgenic animal "will be unpredictable" (emphasis added), does not establish any lack of enablement of the methods of nuclear transfer as instantly claimed. To the contrary, Co *et al.* teaches that satellite DNA-based artificial chromosomes (SATACS) can be successfully delivered to (by pronuclear microinjection) and stably maintained and expressed in transgenic animals, with few inter-species differences (murine *vs.* bovine, *see, e.g.,* pp. 183-184), thus evidencing the **desirability** of using artificial chromosomes in methods for the generation of transgenic animals.

Furthermore, Claim 1 includes the steps of introducing an artificial chromosome into a donor cell and then tranferring the nucleus thereof into an

enucleated recipient. There is no requirement for generating a transgenic animal. Hence, claim 1 is outside the purview of this rejection. Similarly, Claim 2 does not require generation of a transgenic animal.

Applicant therefore respectfully submits that the references cited by the Examiner fail to establish a lack of "predictability" of the methods as instantly claimed. To the contrary, the cited references show that nuclear transfer is feasible and commercially promising, with in fact very low efficiency of nuclear transfer sufficing to establish a transgenic animal line. Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for an area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. § 112, first paragraph, is not a consideration. The relevant standard is not that of an established, fully optimized, method; rather, a patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. There is no requirement that a treatment method achieve a specified level of efficacy or efficiency in order to be considered "enabled" by the specification. In fact, the above references demonstrate that the efficiency of nuclear transfer need not be high to be of commercial value, *e.g.*, in making transgenic animals. Therefore, Applicant respectfully submits that the cited references, regardless of their post-filing date or the purpose for which they were cited, fail to establish that the claimed methods are not enabled.

2) Case Law cited by Applicant is "not relevant."

The Examiner alleges that case law cited by the Applicant as providing the standard for enablement is "not relevant" because the issue is enablement of the full scope of the subject matter as claimed where the state of the art is unpredictable. The Examiner cites case law that is allegedly more apt in the

instant case due to the alleged "unpredictability" of the claimed methods. the case law cited by the Examiner includes: In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938); In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) and In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991); and Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

It is respectfully submitted that, regardless of whether or not the Examiner considers "unpredictability" of the instant methods to provide "reasonable doubt" as to a disclosure being broadly enabling (Ex parte Singh), the inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require *undue experimentation* to make and use the claimed subject matter. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). A consideration of whether or not undue experimentation is required takes into account a number of factors, of which predictability is only **one** factor. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986).

The case law cited by the Applicant in the previous response filed June 18, 2003, provides the standard for enablement (no undue experimentation) and how to apply and measure that standard. The Examiner, on the other hand, appears to be implying that "predictability of the art" alone need be considered in establishing whether the application is enabling for the methods as claimed. While Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991) may stand for the proposition that unpredictability of an art may provide doubt as to a "broad statement" made in support of enablement of claims, the case does not stand

for the proposition that no other factors need be considered in assessing enablement of a disclosure. Moreover, none of the aforementioned cases cited by the Examiner change the standard for assessing enablement, whether the rejection is one of lack of enablement or scope of enablement.

Notwithstanding the above, as discussed herein and previously in the response filed June 18, 2003, the Examiner's arguments in support of the alleged "unpredictability" of the instant methods are (1) the post-filing date art cited by the Examiner that allegedly demonstrates such unpredictability; and (2) that Wilmut *et al.*, described and incorporated by reference in the instant application, is allegedly not an enabling disclosure because the method is "non-reproducible". In response herein and previously, Applicant has shown that (1) the post-filing date art cited by the Examiner in fact demonstrates the promise of nuclear transfer methods and their operability; and (2) the disclosure of Wilmut *et al.* is reproducible for the methods of nuclear transfer described and incorporated by reference in the specification. Therefore, regardless of whether lack of enablement and/or overly broad scope of enablement is alleged on the basis of "unpredictability" alone, or by taking unpredictability into consideration with the other factors enumerated in Ex parte Forman, it is respectfully submitted that the Examiner has failed to establish a level of experimentation beyond routine variation that would render the instant methods "unpredictable" to the extent that the standard for enablement is not met.

In addition, the claims as amended herein specify that the nuclear donor and recipient cells and the host are mammalian. As discussed herein and previously, the teachings of the specification, in light of the advanced knowledge of those of skill in the art of mammalian nuclear transfer and transgenic animal generation as evidenced by numerous publications incorporated by reference in the application and/or provided responsive to the

previous Office Action, are adequately enabling for the scope of the methods as claimed.

3) The Disclosure of Wilmut *et al.* is not Enabling

Responsive to Applicant's argument that the disclosure of Wilmut *et al.* (1997) Nature 385:810-813) is enabling, the Examiner maintains that the process of Wilmut *et al.* "has been found to be non-reproducible in the art." Responsive to Applicant's arguments that the articles of Wolf *et al.* (*J. Biotechnol.*, 65:99-110 (1998)), cited by the Examiner, and Sgamarella *et al.* (*Science*, 279(51):635-636, (1998) cited in Wolf *et al.* and submitted by Applicant along with the previous response, do not demonstrate that undue experimentation would be required to practice the method of Wilmut *et al.*, it is alleged that the arguments are not persuasive because the specification allegedly does not teach how one of skill in the art would have corrected the alleged "problems" of the method of Wilmut *et al.*

The Examiner further alleges that the article of Schnieke *et al.* (*Science*, 278:2130-2133, (1997); WO 02/062131), cited by Applicant in support of the argument that the Wilmut *et al.* method is reproducible, in fact did not "exactly follow" the method of Wilmut *et al.* because "the source of nuclei were different, the culture methods were different, *etc.*," and these "improvisations" are allegedly not taught in the specification.

As discussed below, it is respectfully submitted that the disclosure of Wilmut *et al.* is reproducible and therefore the specification, which describes and incorporates by reference the method of Wilmut *et al.*, need provide no guidance as to how to correct the "problems" of Wilmut *et al.*

a) The disclosure of Wilmut *et al.* is presumptively reproducible and operative.

As discussed in the response filed June 18, 2003, and herein, U.S. Patent No. 6,147,276 is the issued patent corresponding to U.S. Application Serial No. 08/802,282, filed February 19, 1997, which is a continuation of PCT

Application No. PCT/GB96/02099, published as WO 97/07669 and incorporated by reference in the instant application. Further, Wilmut *et al.*, published February 27, 1997, is a publication that is based on the disclosure of WO 97/07669. Because a U.S. Patent has issued with the same disclosure as WO 97/07669, and because a U.S. Patent is presumptively valid and enabled as of its filing date, the disclosure of WO 97/07669 is operative because claims that are based on the disclosure have issued in U.S. Patent No. 6,147,276.

Therefore, contrary to the Examiner's assertions regarding "non-reproducibility" of the method of nuclear transfer described in Wilmut *et al.*, it is respectfully submitted that Wilmut *et al.*, which is based on PCT Publication No. WO 97/07669, which in turn has the same disclosure as that of U.S. Patent No. 6,147,276, is presumed to be operative and reproducible because the issued U.S. patent is presumptively valid (35 U.S.C. 282). Furthermore, the instant specification is reproducible and operative for the methods as claimed because it describes and incorporates by reference the methods of nuclear transfer provided in International PCT Publication Nos. WO 97/07669 and Wilmut *et al.* Furthermore, in light of the above, the specification, which describes a method of nuclear transfer and incorporates by reference WO 97/07669, WO 97/07668 and Wilmut *et al.*, is reproducible and operative for the methods as claimed.

b) Notwithstanding the above, the disclosure of Wilmut *et al.*, and the specification which describes and incorporates by reference the method of Wilmut *et al.*, is enabling for the methods as claimed.

As discussed previously and herein, the relevant question with regard to enablement of the subject matter of the instant claims is whether the particular steps and materials of the claimed methods are described in the specification in such a way as to enable one skilled in the art to make and use the subject matter **as claimed**. The specification describes and incorporates by reference Wilmut et al. (1997) Nature 385:810-813, International PCT application Nos.

WO 97/07669 and WO 97/07668). The specification exemplifies the steps of the methods as instantly claimed in which an artificial chromosome is introduced by any suitable method into an appropriate donor cell, such as a mammary gland cell, is then introduced, such as by cell fusion or microinjection, into an unactivated oöcyte, preferably enucleated cell. The specification provides how enucleation may be effected, how the recipient oöcyte is activated, and how to produce a reconstituted mammalian embryo, which is then introduced into a mammalian host. By following the teachings of the specification as provided herein, one of skill in the art can (1) introduce a chromosome into a nuclear donor cell; (2) transfer the nucleus of the nuclear donor cell into an enucleated non-human mammalian recipient cell of the same species; and (3) further transfer the recipient cell into a maternal mammalian host animal for development of a mammalian animal or fetus therefrom.

This is evidenced by the success of practicing the nuclear transfer steps of the method as demonstrated by Wilmut et al. (1997) Nature 385:810-813, International PCT application Nos. WO 97/07669 and WO 97/07668, incorporated by reference herein. Contrary to the Examiner's assertion that the disclosure in Wilmut *et al.* is not enabling, Wilmut *et al.* (and International PCT application Nos. WO 97/07669 and WO 97/07668) demonstrated that by following the steps of the method as provided in the specification, live lambs born after nuclear transfer from a mammary gland cell were produced. A patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation.

c) Schnieke *et al.* follows the teachings of Wilmut *et al.*

In the previous response filed June 18, 2003, Applicant provided evidence that the methods as claimed, operate as claimed. Applicant provided the references Schnieke *et al.*, *Science*, 278:2130-2133, (1997) and WO

02/062131), which demonstrate that by following the teachings of the application and that of Wilmut *et al.* incorporated therein, nuclear transfer and the generation of transgenic animals is obtained as claimed.

The Examiner alleges that Schnieke *et al.* did not "exactly follow" the method of Wilmut *et al.* because "the source of nuclei were different, the culture methods were different, *etc.*," and these "improvisations" are allegedly not taught in the specification. Applicant respectfully disagrees.

It is respectfully submitted that Schnieke *et al.* specifically states that nuclear transfer was performed as described in Wilmut *et al.* (*see* page 2131, caption for Table 1, and col. 3, second full paragraph). Further, the nuclear transfer is from a donor cell that is a fetal fibroblast cell type, which is one of the cell types used in Wilmut *et al.*, and the recipient enucleated oocyte is derived from Scottish Blackface ewes, which is the same source as that used in Wilmut *et al.* It is requested that the Examiner point to "improvisations" in Schnieke *et al.* that are considered "not routine." To the contrary, variations, if any, between the nuclear transfer methods of Wilmut *et al.* and Schnieke *et al.* are in minor details that are unquestionably routine. Schnieke *et al.* tests the nuclear transfer method of Wilmut *et al.* using a nuclear donor cell that contains a transfected gene - there is no difference in the cell types or steps followed in carrying out nuclear transfer in Schnieke *et al.* compared to the nuclear transfer method taught by Wilmut *et al.*

Therefore, it is respectfully submitted that the reference Schnieke *et al.* demonstrates operativeness of the method of Wilmut *et al.* and of the instant specification, which describes the method of Wilmut *et al.* and incorporates it by reference. Schnieke *et al.* demonstrates that by following the teachings of Wilmut *et al.* and of the instant application, (1) fetal fibroblasts can be transfected with genes, such as human Factor IX; and (2) live transgenic sheep encoding human Factor IX can be produced by nuclear transfer of the nucleus

from the fetal fibroblast into enucleated sheep oocytes (*e.g.*, Table 1 at page 2131).

On the other hand, Wolf *et al.*, cited by the Examiner as establishing that the method has not been reproducible in other laboratories, merely questions the reproducibility of the result in Wilmut *et al.* There is no demonstration in Wolf *et al.* that the method of Wilmut *et al.* is not reproducible, nor that the experimentation required to reproduce the method of Wilmut *et al.* would be undue.

Wolf *et al.* cites Sgamarella *et al.* (*Science*, 279(51):635-636, (1998); attached hereto) for its assertions regarding the alleged non-reproducibility of the method of Wilmut *et al.* A review of Sgamarella *et al.* indicates that this reference is critical of the success of Wilmut *et al.*, but again provides no evidence demonstrating that the disclosure of Wilmut *et al.* is not enabling. Sgamarella *et al.* is skeptical of the reproducibility of the method of Wilmut *et al.* only because Wilmut allegedly announced that he had no intention of practicing the method again. Sgamarella *et al.* further expresses skepticism because a subsequent publication of Wilmut used a fetal cell rather than an adult cell in a nuclear transfer method, leading Sgamarella *et al.* to question whether Wilmut *et al.* used an adult cell and, if so, why "Dolly's" mitochondrial DNA was not analyzed to establish the same.

Neither an alleged decision by Wilmut not to practice the method of Wilmut *et al.* again, nor any of the allegations in Sgamarella *et al.* provide any evidence that the disclosure in Wilmut *et al.* is not enabling. Furthermore, the Examiner provides no basis for this assertion regarding the state of mind of Wilmut *et al.*, and absent evidence supporting it, such statement regarding Wilmut's alleged decision cannot be sustained. In fact, as provided responsive to the previous Office Action, in a paragraph immediately following the article by Sgamarella *et al.*, Wilmut provided explanations for each of the allegations in Sgamarella *et al.* (*e.g.*, why "Dolly" could only have been derived from cells

derived from adult mammary glands, why no fetal metarial was retained for analysis, an affirmation that the method worked) that refute any speculation as to his state of mind or the reproducibility of his experiments.

Unlike Schnieke *et al.* and International Publication WO 02/062131, provided by Applicant responsive to the previous Office Action, the reference Wolf *et al.* cited by the Examiner does not carry out the method of Wilmut *et al.* to demonstrate whether or not it is operative; Wolf *et al.* merely speculates about the reproducibility of Wilmut *et al.* Therefore, it is respectfully submitted that the Examiner has failed to provide evidence that the method of Wilmut *et al.* is not reproducible, nor has the Examiner pointed to basis in Schnieke *et al.* or International Publication WO 02/062131, provided by Applicant responsive to the previous Office Action, for the assertion that these references engage in experimentation relative to Wilmut *et al.* that is "non-routine."

4) Lack of working examples, and knowledge of those of skill in the art with respect to nuclear transfer

The Examiner alleges that Applicant has failed to demonstrate that the art of making transgenic animals by nuclear transfer involving introducing the gene of interest into a cell using artificial chromosomes was routine as of the filing date. It is further alleged that no working examples are provided showing how to make a transgenic animal as recited in the claimed methods.

Lack of working examples

It is respectfully submitted that when considering the factors relating to a determination of enablement, if all the other factors point toward enablement, then the absence of working examples by itself will not render the disclosure non-enabling (MPEP 2164.02). As discussed above and previously, Applicant has demonstrated in great detail that the specification teaches each step of the claimed methods which, when combined with the advanced state of the art in methods of nuclear transfer and generating transgenic animals at the time the

instant application was filed, renders the specification adequately enabling for the full scope of the methods as claimed.

Moreover, as discussed in the response filed June 18, 2003, the specification provides numerous working examples demonstrating each of the steps of the instantly claimed methods including isolation and use of artificial chromosomes containing heterologous nucleic acid, the introduction of these artificial chromosomes into cells and the generation of transgenic animals from these cells containing artificial chromosomes.

The Examiner alleges that no working example is provided showing the generation of a transgenic animal by nuclear transfer using a donor nucleus containing an artificial chromosome. Applicant has, however, provided numerous working examples showing that artificial chromosomes encoding genes can be introduced into cells, stably expressed therein, and used to generate transgenic animals (*see, e.g.*, Example 13, at page 165 of the specification, describes methods for the microinjection of artificial chromosomes into eukaryotic cells, and detection of expression of the encoded heterologous DNA (βGal) in cells injected with the DNA. Example 14, at page 168 of the specification, describes in great detail the development of transgenic mice expressing the anti-HIV ribozyme encoded by an artificial megachromosome. Example 14 also describes in great detail the uses of the artificial chromosomes in generating transgenic animals). Therefore, it is respectfully submitted that the teachings of the specification, when combined with the working examples provided therein, the knowledge of those of skill in the art and the other factors enumerated in Ex parte Forman, is adequately enabling without a single working example that includes all of the steps of the various instantly claimed methods.

Knowledge of those of skill in the art with respect to nuclear transfer

As discussed previously and herein, at the time of filing of the instant application, a broad body of knowledge had amassed in the area of nuclear transfer. Contrary to the Examiner's assertion and as discussed above and

previously, methods of nuclear transfer, including transfer of donor cells containing exogenously introduced nucleic acids, and methods for the generation of transgenic animals therefrom were known and extensively practiced by those of skill in the art at the earliest priority date of the instant methods or shortly thereafter (*see*, Wilmut *et al.* (1997) *Nature* 385:810-813, International PCT application Nos. WO 97/07669 and WO 97/07668; Wells *et al.*, *Biol. Reprod.*, 57:385-393 (1997); Campbell *et al.* (1996) *Nature 380*:64-66; PCT Application Publication No. WO95/17500; Solter (1996) *Nature*, 380: 24-25; Sims *et al.* (1993), *Proc. Natl. Acad. Sci. USA*, 90:6143-6147; Tanaka *et al.* (1997) *Animal Reprod. Sci.*, 49:113-123; Schnieke *et al.*, *Science*, 278:2130-2133, (1997)).

As discussed above, the methods of Wilmut *et al.* (1997) *Nature* 385:810-813, International PCT application Nos. WO 97/07669 and WO 97/07668, which are described and incorporated by reference in the instant application, are reproducible for the generation of transgenic animals of a variety of mammalian. Moreover, these methods are reproducible and operate as claimed, as evidenced by the publications Schnieke *et al.* (*Science*, 278:2130-2133, (1997); WO 02/062131) discussed previously and herein and provided responsive to the previous Office Action. The remaining references cited above were provided responsive to the previous Office Action and demonstrate the generation of transgenic mammals of a variety of species, such as bovines, ovines and ungulates, using nuclear transfer methods.

Responsive to the Examiner's allegation that the generation of transgenic animals using nuclear transfer methods where the donor nucleus contained an artificial chromosome was not routine, it is respectfully submitted that Applicant has demonstrated the advanced knowledge of those of skill in the art at the time the instant application was filed with respect to each of the steps of the methods as claimed, including (1) introducing artificial chromosomes into cells and obtaining stable expression of their encoded genes; and (2) nuclear transfer

methods. Therefore, it is respectfully submitted that given the advanced knowledge of those of skill in the art with respect to each of the steps of the instantly claimed methods at the time the instant application was filed, and given the extensive teachings in the specification with respect to each of the steps, the specification in light of the knowledge of those of skill in the art and the other factors enumerated in Ex parte Forman is adequately enabling for the methods as claimed.

Further, to evidence that a method for generating mammalian transgenic animals using nuclear transfer methods where the donor nucleus contains an artificial chromosome as claimed herein, operates as claimed, Applicant provided publications (Schnieke *et al.*, *Science*, 278:2130-2133, (1997); WO 02/062131) responsive to the previous Office Action demonstrating that by following the teachings of the application and that of Wilmut *et al.* incorporated therein, nuclear transfer and the generation of mammalian transgenic animals is obtained as claimed.

Also, although these publications rebut assertions of inoperativeness, they also further evidence enablement. It is noted that the level of skill in the biotechnical arts is recognized to be high (see, *e.g.*, *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986). Further, as discussed below, methods for performing the various steps of the claimed methods, such as introducing nucleic acids including chromosomes into nuclear donor cells, transferring the nuclei of the nuclear donor cells into recipient cells and allowing the recipient cell to develop into a transgenic fetus or animal in a host are known to the skilled artisan.

The reference Schnieke *et al.* demonstrates that by following the steps of nuclear transfer of Wilmut *et al.*, live transgenic sheep encoding human Factor IX were produced (*e.g.*, Table 1 at page 2131). The International Publication WO 02/062131 demonstrates that by following the steps of the method as taught in the instant specification (1) artificial chromosomes such as SATACS

can be generated and introduced into nuclear donor cells; and (2) the nucleus of the nuclear donor cell can be transferred to into an enucleated recipient cell to yield bovine blastocysts. These blastocysts can then be placed in extended embryo culture and are capable of generating animals (bovines) (Examples 1-3, *e.g.*, beginning at page 55 of the specification).

In summary, the specification enables one of skill in the art to, by following the methods set forth therein, generate artificial chromosomes, readily identify the resulting artificial chromosomes based on the detailed characterization provided in the specification, incorporate foreign nucleic acid, e.g., heterologous DNA encoding a therapeutic product, into an artificial chromosome, and isolate and transfer artificial chromosomes for use in other cells and systems, including the generation of transgenic animals by nuclear transfer and other such methods. By virtue of Applicant's discovery of artificial chromosomes and the teachings of the specification, those of ordinary skill in the art are able, without undue experimentation, to make and use the artificial chromosomes and to combine the artificial chromosomes with known recombinant DNA procedures, many of which are referenced in the specification, to achieve any number of particular outcomes, including the introduction and stable maintenance of artificial chromosomes in cells, such as nuclear donor cells and obtaining transgenic animals by nuclear transfer and other such methods.

B. Conclusion

As discussed above and in the previous response filed June 18, 2003, which is incorporated by reference herein, Applicant respectfully maintains that a consideration of the factors enumerated in Ex parte Forman leads to the conclusion that undue experimentation would not be required to introduce an artificial chromosome into a nuclear donor cell, transfer the nucleus of the nuclear donor cell into an enucleated recipient cell and further permit the recipient cell to develop into an animal or fetus in a host. The application

teaches a broad method for introduction of satellite artificial chromosomes into nuclear donor cells that is not limited by the species of satellite artificial chromosome or species of cell. The application further teaches nuclear transfer of the nuclear donor cell nucleus into an enucleated recipient cell and development of the resulting recipient cell into an animal. Therefore, Applicant respectfully maintains that the instant application teaches how to make and use methods that are commensurate in scope with the instant claims.

As discussed above and previously, it is respectfully submitted that the Examiner has not demonstrated "unpredictability" of the method of Wilmut *et al.* which, either alone or in combination with the other factors recited in Ex parte Forman, would render the instant disclosure not enabling for the methods as claimed. Contrary to the Examiner's assertion and as discussed in detail above, Applicant has demonstrated that the methods of the specification, which describes and incorporates the methods of Wilmut *et al.* and WO 97/07669 by provides an enabling disclosure because no more than routine experimentation is required to reproduce the teachings of the specification. Applicant has further demonstrated that the disclosures of Wilmut *et al.* and WO 97/07669 are presumptively reproducible and operative because issued U.S. Patent No. 6,147,276, which has the same disclosure as WO 97/07669 (incorporated by reference in the instant application and also related to the disclosure of Wilmut *et al.*) and has issued claims based on its disclosure, is presumptively valid and enabled. Therefore, the methods of the specification, which describes and incorporates by reference the methods of nuclear transfer of WO 97/07669 and Wilmut *et al.*, are reproducible and operative.

In light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the fact that it is predictable that artificial chromosomes can be introduced into cells and can be further used to generate transgenic animals by various methods such as nuclear transfer, and the breadth of the claims, it

would not require undue experimentation for one of skill in the art to practice the claimed methods.

Accordingly, a consideration of the factors enumerated in Ex parte Forman leads to the conclusion that undue experimentation would not be required to introduce an artificial chromosome into a nuclear donor cell, transfer the nucleus of the nuclear donor cell into an enucleated recipient cell and further permit the recipient cell to develop into an animal or fetus in a host.

Policy Considerations

In addition to the above, it is clear that Applicant's discovery is of a pioneering nature, and, as such, is entitled to broad claim protection.

As taught in the above-captioned application, any methods known in the art pertaining to introduction of foreign genes carried in traditional, standard sources (such as genes harbored in expression vectors) into cells for any variety of purposes, e.g.,, gene therapy, protein production and the generation of transgenic animals, including nuclear transfer methods, may be applied in similar fashion to the introduction of artificial chromosomes, particularly SATACs and minichromosomes, into cells. The application describes and demonstrates that once the artificial chromosomes are generated and isolated and/or introduced into cells, then any known procedure that has previously been carried out with any heterologous gene from any source is applicable to utilization of artificial chromosomes carrying foreign genes of interest. The application is replete with descriptions of numerous uses of SATACs and minichromosomes. The descriptions of the many ways in which the artificial chromosomes may be used include references to reported procedures for introducing exogenous nucleic acids into cells.

It is therefore respectfully submitted that the claims directed to methods of nuclear transfer and, further, producing transgenic animals using SATACs and minichromosomes, are commensurate in scope with the discovery and its

disclosure within the above-captioned application. It would be unfair and contrary to the Constitutional mandate set forth in Article, Section 8, to deprive Applicant of protection of the broad applications of the pioneering discovery disclosed and described in exhaustive detail in the subject application.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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